

SERUMS AND SERUM-THERAPY.

THE increasing therapeutic use of the serum of animals immunised by bacteria and bacterial products, is one of the most remarkable characteristics of modern medicine. The reports of recent years prove that, in diphtheria at least, the antitoxic treatment has very markedly reduced the percentage mortality. Whether the expectation that similar results should follow the application of serum therapeutics to other diseases will be realised, it is not possible at present to say.

Diphtheria Antitoxic Serum.

When susceptible animals are repeatedly injected with filtered cultures of the diphtheria bacillus, they, after a time, acquire an "immunity" by which, according to its completeness, they are rendered either partially or wholly insusceptible to the action either of the diphtheria bacillus or of its poisons. Experience shows that serum from animals possessing this acquired immunity has a greater or less power of neutralising diphtheria toxine in vitro; and, when injected into other animals, of conferring a temporary immunity on them. It also exerts direct curative action when given to animals already suffering from the effects of diphtheria toxine. It has, however, been shown that the immunity of an animal, and the antitoxic power of its serum, do not necessarily go hand-in-hand, and that some horses, whose immunity is great, furnish a serum of only very low antitoxic or curative power.

Definition of the Antitoxine Unit.

Diphtheria antitoxic serum is standardised in this country according to the German method. In its earlier form, series of guinea pigs of 250 gm. weight were injected with ten times the minimal fatal dose of a filtered broth culture (fatal in 48 hours) mixed with varying quantities of serum. The smallest quantity of the latter which would protect from all consequences, both local as well as general, formed the measure of its

The accompanying table shows clearly a regular percentage decrease in mortality *pari passu* with a regular increase in the percentage of cases treated with antitoxine.

Year.	Cases of Diphtheria treated in the Hospitals of the Metropolitan Asylums Board.	
	Antitoxine treated cases, per cent. of all cases.	Mortality, per cent. of all cases.
1888-1895.	...	28.5
1894.	...	29.6
1895.	61.8	22.5
1896.	71.3	20.8
1897.	80.2	17.5
1898.	81.4	15.5
1899.	...	13.95
1900.	...	12.01

The reader seeking further statistics may profitably refer to the following articles, wherein further convincing figures will be found :—

“Tabulation of results in Laryngeal Diphtheria,” *Medical Chronicle*, March, 1898.

“Results in London Fever Hospitals,” *British Medical Journal*, Vol. I., 1899, fol. 197, 268.

“Summary of results,” by Dr. Marsden, *British Medical Journal*, Vol. II., 1900, fol. 658.

“Conclusions formed after 6 years’ experience with the antitoxine treatment of Diphtheria,” *Medical News*, New York, January 19th, 1901.

An exhaustive article in *The Therapist* for February 15th, 1901.

Experiments on animals have shown that the amount of antitoxine which is necessary to save life increases with astonishing rapidity according to the length of time which elapses between the injection of the diphtheria virus and the administration of the curative serum: and this is amply confirmed by the results of experience in hospitals. Thus Wernicke and Behring having determined the amount of antitoxic serum necessary to save from death a guinea pig which had immediately before been injected

subcutaneously with a lethal dose of diphtheria toxine, found that ten times this amount was required to effect a cure if its administration was deferred until eight hours after the injection of the toxine ; whilst twenty-four hours afterwards fifty times the initial quantity was necessary.

The Metropolitan Asylums Board Report states that the only limit to the administration of antitoxine is the bulk of the fluid in which it is contained. Therefore a large dose should be given at the earliest possible moment whenever there is reason to suspect diphtheria ; and, in cases which progress unfavourably, the treatment may be repeated in about six hours. Far less, however, is to be expected from repeated injections at intervals than from one strong dose given at the outset of the attack. In no case should either the administration of antitoxine, or the repetition of the dose, be delayed until the result of a bacterial examination has been made known.

Dose.

The dose for a case of moderate severity should be not less than 2,000 units, and, in severe cases, 4,000 units at least should be given at once. These doses should be given irrespective of age, because diphtheria is very fatal to young children. If any difference were to be made, adults would have the smaller doses, as the prognosis in diphtheria improves with the age of the patient.

As the question of the keeping quality of serums is frequently raised, it may be stated generally that, provided they are kept in a cool place and protected from light, and are not opened, these serums may be relied upon to remain practically unaltered for at least a year from the date of issue. While they should be kept in a cool place, they should not be exposed to frost.

Now that the Serums prepared at the Wellcome Physiological Research Laboratories are issued in hermetically sealed phials, their keeping quality is considerably enhanced, so that, if stored under suitable conditions, they may be relied upon to keep for a considerable period.

In some cases, the administration of diphtheria antitoxic serum is followed by rashes, transitory rise of temperature, and occasionally pains and swellings in the joints. These accidents have been shown to be also

caused by normal horse serum, so that they are not in any way to be attributed to the antitoxine itself. The introduction of more highly potent serums, thus allowing a diminution of the bulk to be injected, has rendered these complications less frequent. They arise for the most part during convalescence, and do not appear to have resulted in any case in death, though they have doubtless sometimes retarded recovery.

Directions for Use of Diphtheria Antitoxic Serum (Wellcome).

Keep in a cool, dark place, and protect from extremes of either heat or cold.

To open the phial, break off the tube at the file-mark near the lower margin of the label.

Inject under the skin. Do not inject into the arm, or any part liable to much movement. The best point for injection is either between the scapulæ, or under the skin of the abdomen. Allow the serum to become absorbed naturally; the swelling over the point of injection will disappear without external manipulation.

The most careful antiseptic precautions should be observed. The skin about the place where the injection is to be made should be sterilised by rubbing it, first with soap and water, next with ether (to remove grease), and finally with 1 in 20 solution of carbolic acid. Sterilise the syringe, after carefully cleaning it, by boiling for a few minutes in water.

Commence the serum treatment immediately the case is suspected to be one of diphtheria, and inject the contents of one phial at once. As many as 4,000 units may with advantage be given at the first injection in severe cases. Statistics show that success is almost certain if the serum treatment be commenced early enough. Every day's delay lessens the chances of success.

The serum may be used freely. In cases which proceed unfavourably, the treatment may be repeated in about six hours.

Protective injections may with advantage be administered to the rest of the family, wherein one member has been attacked with diphtheria. The whole of the contents of one phial may be injected in each case.

Bacterial Diagnosis of Diphtheria.

Immediate steps should be taken to confirm the diagnosis by bacteriological methods. The Wellcome Physiological Research Laboratories offer every facility to medical men who have not ready access to a bacteriological laboratory, and for a fee of 2/6 (or 3/- if a telegraphic report be required) undertake to have membrane and other suspected substances examined and reported on.

Burroughs Wellcome & Co. issue a new and improved outfit, designed to meet the Post Office regulations, at a charge of sixpence. In order to avoid waste of time in urgent cases, medical men would do well always to provide themselves with these outfits, thus securing instant despatch of suspected specimens to the laboratories for examination.

Directions for using Diagnosis Outfits.

1. Open the case containing the diagnosis outfit by detaching plaster on one side, and withdraw tube.
2. Place the patient in a good light; withdraw the swab from the tube; depress the tongue well with a perfectly clean depressor; and rub the swab well over the affected part.
3. If possible rub underneath any membrane or slough that may be present.
4. Do not soil the mouth of the tube in replacing the swab.
5. Replace the tube in the case; close the case by means of the plaster, pack it in the envelope, and forward it, with fee of 2/6 (or 3 - if telegraphic report be required), to The Director, Wellcome Physiological Research Laboratories, Brockwell Hall, Herne Hill, London, S.E.

Anti-tetanus Serum.

This serum, like anti-diphtheria serum, is antitoxic in its action. Although it may be stated that some cases of this disease have, without doubt, been distinctly benefited by its administration, yet, in many others, the remedy has failed; and a consideration of the nature of the disease

shows why this is so, and why, even more so than in diphtheria, it is necessary to commence the treatment at the earliest possible moment.

Tetanus is a disease caused by the action of the toxine of the bacillus tetani upon the central nervous system ; the toxine, as in the case of diphtheria, being produced in some local lesion, the seat of the growth and multiplication of the specific organisms. In tetanus, the toxine makes its way to the motor ganglion cells, partly by way of the nerves in connection with the affected part, and partly by way of the blood.

Unfortunately the convulsive stage of tetanus is an indication not of the commencement of the disease, as is the appearance of a membrane in diphtheria, but of a comparatively advanced stage in the affection, and of the progress of the above mentioned changes in the nervous system. The remedy should therefore be administered immediately on the manifestation of any distinct symptoms possibly tetanic, such as difficulty in opening the mouth, stiffness in the neck, or the onset, some days after the accident and without obvious cause, of an acute pain at the point of injury ; and in view of the fact that the tetanus bacillus is localised and restricted to the seat of infection, attention is called to the advantage, in cases of punctured wounds, of excising freely and thoroughly the tissues around. The curative dose of anti-tetanus serum may vary from 50 c.c. to 100 c.c. in one dose or more, but, as a prophylactic in the treatment of wounds contaminated with dust, dirt, soil, etc., a small dose of the antitoxine, say 5 c.c. (*i.e.*, about 85 minims), is said to be sufficient. The protection, however, will not persist longer than five or six weeks, so that at the end of that period the injection should be repeated. It should be remembered, in considering doses, that it is impossible at present to state definitely the quantity of serum necessary to meet a given case, for so much depends on the severity of the attack, and the stage at which treatment is begun. It is, therefore, better to give a large dose at the commencement. The old medicinal treatment should not be neglected.

The records of 98 cases treated by serum were collected by Weischer (*Münch. med. Woch.*, 16th November, 1897). Of these 41 died, the mortality per cent. thus being 41.8.

The serum has been injected directly into the substance of the brain with success ; and it has been claimed that this method gives the surest hopes of benefit from the treatment. A full account of this, giving details of the operation, may be found in the *Brit. Med. Journal* for January 7th. 1899.

Anti-streptococcus Serum.

When the streptococcus erysipelatis and the streptococcus pyogenes were first described by Fehleisen and Rosenbach respectively, it was thought that these organisms could be readily distinguished from one another. Further experience, however, soon showed that the cultural characters which the authors described are variable, and it is now generally agreed that these organisms cannot be distinguished by any cultural or morphological differences. Moreover, the lesions provoked by them, when injected into animals, appear to vary only with differences of the seat and method of inoculation, the resistance of the animal, and more particularly with the virulence of the micro-organism, which latter can be altered at will. This in itself forms no decisive evidence of their identity, for similar lesions can be produced by other organisms, which are entirely distinct from the streptococci. For example, Koch, in his work on wound infections, describes a bacillus which caused an erysipelatous process in the rabbit's ear, and many other organisms will do the same thing. More satisfactory evidence, based upon bacterial examination of instances of disease in man, has been advanced by Petruschky. (Zeit. f. Hyg. 1896.) This careful investigator, who has devoted many years' study to the streptococci, finds that the various streptococcal infections in man pass into one another, or arise one from another. As an example he quotes the case of an infant who suffered from erysipelas, in consequence of a scratch in the nasolabial fold, becoming infected from its mother who was suffering from mastitis which had no erysipelatous character. Further, he had the opportunity of producing in human beings typical erysipelas with a streptococcus obtained from a case of peritonitis following on a parametritis; and he has been finally led to conclude that the streptococcus erysipelatis and the streptococcus pyogenes are essentially identical. A similar conclusion has been reached by Marmorek, and it seemed probable that the identity of these organisms would soon be an accepted fact. More recently, however, Van de Velde (Archiv. de Méd. expérimentale, tom. IX., No. 4, 1897) has brought forward evidence which entirely re-opens the question. In a most careful and laborious series of experiments, which no one can study without the conviction that they afford evidence of very great weight, he has demonstrated the existence of important differences between streptococci of different origin. Having started with two races of streptococci, A and P, and having immunised a horse with each, he obtained two serums, A and P, each of which possessed remarkable powers of protecting rabbits against the particular streptococcus

which had been used for the production of that serum ; but, while serum A had some slight power of protecting against streptococcus P, serum P had absolutely no power of protecting against streptococcus A. Moreover, serum A had no power of protecting against two other streptococci M and D, the virulence of which was low, nor against Marmorek's very virulent streptococcus. But it had some power against another equally virulent streptococcus, though the evidence of this last fact is not very satisfactory. He then immunised a horse with streptococcus A and streptococcus P, and found that the serum would protect against both organisms. He therefore suggests that in order to produce a satisfactory therapeutic serum, horses should be treated with as many races of streptococci as possible. Further, he showed that the power which an anti-streptococcus serum possesses of clumping streptococci, in the same way as an anti-typhoid serum will clump the typhoid bacilli, go hand-in-hand with its power of protecting animals against the streptococcus in question. It follows from this that if one is called upon to treat a case of streptococcal disease, and can isolate the organism, it will be possible to ascertain whether a particular serum is likely to be of any therapeutic value.

A fairly large amount of anti-streptococcus serum, prepared by treating horses as indicated above, has been used by medical men during the past two years in the treatment of various septicæmic conditions. Judging by the published accounts, which have appeared from time to time, its administration has been followed by very beneficial results in many instances. Briefly stated, the results obtained with this serum have by no means been so disappointing and uncertain as those obtained with anti-typhoid serum ; while they have fallen short of the brilliant results obtained by the early use of diphtheria antitoxic serum.

Anti-typhoid Serum.

After an extended trial it has been decided that this serum, as at present produced, is not a specific remedy for enteric fever in the human subject. Although in some instances it appears to have done good, in others it has plainly had no beneficial effect. The production of an anti-typhoid serum has, therefore, been temporarily suspended.

The Serum Diagnosis of Typhoid Fever.

A series of investigations made in different countries has gradually brought to light the fact that the serum of an animal rendered highly immune to the typhoid bacillus has a marked action upon the organisms,

causing them to lose their motility, and to become collected together into little masses, which rapidly sink to the bottom of the tube containing the mixture of serum and culture.

Following this, the fact that the serum of patients suffering from typhoid fever gives a reaction with cultures of the typhoid bacillus, similar to, though less marked than, that given by the serum of animals immunised by the bacillus, has been confirmed by a host of observers. This affords fresh evidence of very great weight, that the bacillus typhi is really the cause of typhoid fever, and it also affords a valuable method of diagnosis.

In the serum of those suffering from typhoid fever the reaction is said to have been observed as early as the fourth day. Usually it appears about the beginning of the second week, but it is undoubtedly often absent at this period. According to Courmont (*Revue de Médecine*, October, 1897), it is in cases which are exceptional, either on account of complications or severity, or because they are extremely mild, that the agglutinative power is feeble or delayed; in simple cases of moderate severity it appears constantly about the sixth or seventh day, is active in dilution of 1 in 100 about the tenth day, undergoes a more or less rapid rise towards the end of the febrile period (critical rise), and then disappears more or less rapidly. The persistence of the agglutinative power after recovery appears to be very variable, in some cases rapidly disappearing, in others remaining for years. The blood of those who are not suffering from typhoid fever, and from whom no history of this disease can be obtained, occasionally gives a reaction in dilution of 1 in 10, or even of 1 in 30 (the dilutions recommended by Widal). But these instances do not appear to be sufficiently numerous to seriously impair the value of the test. It is thought desirable, however, to use higher dilutions, viz. :—1 in 50.

From the considerations briefly set out above it seems permissible to conclude that—(1) a negative reaction is of little value in the early days of the fever. It is of greater importance in proportion to the lateness of the period at which it is observed. It can, however, never absolutely exclude typhoid fever. (2) A positive reaction on the other hand, except with dilutions of less than 1 in 40, is sound evidence of typhoid fever present or past. The latter can be excluded if several quantitative tests have been made at different periods, and decided changes in the agglutinative power observed.

Burroughs Wellcome & Co. undertake to have specimens of blood, from suspected cases, examined and reported upon. The necessary outfit, with directions for the proper collection of the blood, and full particulars, is supplied to the medical profession at a charge of sixpence each. A fee of 2s. 6d. is charged for the examination of each case.

Anti-typhoid Vaccine.

The question of the value of anti-typhoid vaccine as a prophylactic against enteric fever is still unanswered, as the evidence which has already been collected is altogether insufficient to enable one to arrive at any definite conclusion. The meagre statistics that have as yet appeared would seem to be in its favour, but it must be frankly stated that considerable doubt exists in the minds of those well able to judge as to the benefits to be derived by means of this vaccine. When the results of the recent inoculations among the military forces in Africa have been carefully collected and tabulated, we may be able to judge more accurately what amount of protection, if any, is conferred by means of the new prophylactic.

Leprosy.

It was placed on record at the Leprosy Conference, held in Berlin, October, 1897, that "the treatment of leprosy up to the present time has had only palliative results. Serum-therapy, so far, cannot be said to have been successful." It appears that this is still the position of serum-therapy as regards this disease. The epitome of current medical literature, *British Medical Journal*, January 26th, 1901, contains an important paragraph dealing with the treatment of leprosy in Norway. "Many points of interest" in "Lie's reports . . . on the No. 1 Leprosy Hospital, in Bergen, for the years 1895-98" are referred to. Amongst others it is stated that "Three lepers were treated with Carrasquilla's serum . . . without benefit."

Yellow Fever.

In the "Annales de L'Institut Pasteur," No. 5, 25 May, 1898, Dr. Sanarelli gives a resumé of the results of his treatment of yellow fever by his "anti-amaril" serum. This serum is bactericidal, not

antitoxic in action; and the author points out that, as at present prepared, it is far more useful as a prophylactic than as a curative agent. In fact, the "anti-amaril" serum can act effectively only when the quantity of poison already formed in the organism (the patient) does not amount to a fatal dose. He goes on to say that the ideas about this disease held by European medical men, who often compare it to cholera, and imagine that the principal lesion is a specific gastro-enteritis, are far from correct. Yellow fever really belongs to the typhus group of diseases, and often presents very serious symptoms due to the action, by way of the circulation, of the amaril poison upon the kidneys and nervous system.

In all he has treated 22 cases, of which 5 died, the mortality being thus 27 per cent. As the case mortality among the indigenous population, and those who are more or less acclimatised by residence in the country, is 50-60 per cent., and no less than 80-90 per cent. among newly arrived Europeans, he considers these initial results, having due regard to small figures, very encouraging. The prophylactic power of the serum was tested with marked success, though on a small scale, in a prison where an epidemic of yellow fever had broken out, and was spreading in spite of isolation and disinfection. After all the prisoners and warders had been injected with the serum, not a single fresh case occurred.

Antivenene.

This serum continues to maintain its claim to be a trustworthy remedy for snake-bite if injected not later than three or four hours after the bite. A case reported in the *Lancet* of 5th January, 1901, illustrates the efficacy of fresh antivenom serum, even after the appearance of general symptoms, and in the absence of any local treatment except sucking the wound. The serum was injected into each flank about $3\frac{1}{2}$ hours after the bite.

Pneumonia.

It should be remembered that this is a general name, and that it includes a number of instances of lung disease which are not all associated with the growth and multiplication in the affected tissues of the same microbe. Anti-pneumococcus serum is a bactericidal, not an antitoxic agent, and might be expected to work beneficially in cases of croupous pneumonia only. The limited number of recorded cases treated with this serum do not appear to bear out the good hopes which were at first entertained of it.

Tuberculosis.

The serum treatment of phthisis has not, so far, given very encouraging results. In fact, there appears to be a fairly general agreement that the cure of this disease is still a matter mainly of hygiene and environment.

ANTITOXIC SERUMS

and other Physiological Preparations

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All home orders for these Serums should be addressed to the Head Offices :—
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	Per Phial.		Per Phial.
Diphtheria Antitoxic Serum ('Wellcome'); HIGH POTENCY, in hermetically-sealed phials containing 4,000 Ehrlich-Behring units, in 5 c.c. or less	7/6	Normal Horse-Serum, 10 c.c.	1/0
Diphtheria Antitoxic Serum ('Wellcome'); in hermetically-sealed phials containing 2,000 Ehrlich-Behring units	2/6	Anti-tetanus Serum, Liquid	6/0
Diphtheria Antitoxic Serum ('Wellcome'); in hermetically-sealed phials containing 1,000 Ehrlich-Behring units	1/3	Anti-tetanus Serum, Dried	10/0
Anti-streptococcus Serum ('Wellcome'); in phials containing 10 c.c.	2/6	Anti-Plague Serum	6/6
Anti-tetanus Serum, Liquid ; in phials containing 10 c.c.	6/0	Anti-Plague Vaccine (prophylactic) ...	6/6
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Anti-venom Serum, Liquid , in phials containing 10 c.c.	5/0	Anti-pneumococcus Serum, No. 1 ...	5/0
		Anti-pneumococcus Serum, No. 2 ...	12/0
		Mallein (for Veterinary Tests)	0/10
		Tuberculin, „ „	0/7

Medical men have pointed out that when ordering Therapeutic Serums by telegram, it is often very undesirable to use the words Diphtheria, Typhoid, etc., or to make any reference to the nature of the illness. In response to these suggestions the following telegraphic code words have been adopted:—

‘MURES’ ... for Diphtheria Antitoxic Serum (‘Wellcome’).
 ‘EPTO’ ... for Anti-streptococcus Serum (‘Wellcome’).
 ‘SUNAT’ ... for Anti-tetanus Serum.
 ‘NOMO’ ... for Anti-venom Serum.

Thus a telegram reading, “‘Tabloid,’ London, send six ‘Mures,’” would be understood to mean—“Burroughs Wellcome & Co., London, send six phials of Diphtheria Antitoxic Serum (‘Wellcome’), containing 2,000 Ehrlich-Behring immunity units.”

If the High Potency Diphtheria Antitoxic Serum (‘Wellcome’) be desired, it should be specially indicated as “POTENT MURES,” or the lower strength by the addition of the words “1000 units” to the telegram.

Specimens for Bacteriological Examination.

All specimens for bacteriological examination, if sent by post, should always be packed in accordance with the special postal regulations governing the transmission of pathological material, and should be addressed to—

The Director,

Wellcome Physiological Research Laboratories,

Brockwell Hall, Herne Hill, London, S.E.

The following fees are charged for examination of, and report on specimens; if a telegraphic report be required, sixpence extra will be charged.

Examination for Diphtheria b.	...	...	...	2/6
„ „ Gonococci	...	...	...	2/6
„ „ Tubercle b.	...	...	...	2/6
Typhoid Diagnosis (Widal test)	...	...	...	2/6

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